and the following discussion.

Objection to Claims Rejection under 35 USC 103(a) as being unpatentable over the Combined Teachings of Dempski et al (US Pat. No. 4,900,755, collectively "Dempski") and Conte et al (US Pat. No.5,738,874, collectively "Conte").

A. Dempski.

Dempski's controlled release form of carbidopa-levodopa is flawed by a delay in onset of action, a condition corrected in the present invention by combining immediate and sustained release principles for optimal therapeutic effects.

B. Conte.

The Examiner states that "Conte teaches a pharmaceutical tablet capable of releasing one or more drugs at different release rates". It is believed this statement is misleading and inaccurate for the following reasons:

1. The prior art contains numerous examples of one or more drugs released at different rates, such as Lin et al (J Int Med Res 10(2):126-128, 1982) and Nomeir et al (J Clin Pharmacol 36(10):923-930,1996). Both abstracts enclosed.

2. Conte incorrectly states (col. 2, lines 3-6) that "the prior art does not envisage the possibility of obtaining products capable of releasing one or

more drugs at different rates or else of releasing two drugs sequentially. See B1 above.

3. Accordingly, Conte did not provide complete and adequate prior art background information. See B1 above.

4. Unlike the novel rationale presented in the current application (see A above), Conte cites no valid or original arguments to support a multiple release format for carbidopa-levodopa use in the treatment of Parkinson's disease. Instead, his explanations merely repeat well known and established facts about levodopa (eg, its metabolism to dopamine and the inhibition of this reaction by carbidopa, col. 2, lines 42-65) that were therapeutically relevant more than twenty years ago and are described in the popular textbook, Goodman and Gilman's The Pharmacological Basis of Therapeutics, Pergamon Press, New York,NY, 8th ED, pp. 466-472, 1990.

5. Neither Conte nor Dempski have recognized the actual problem solved by the current invention, ie, the urgent medical need for immediate as well as long lasting therapeutic action of carbidopa-levodopa in Parkinson's disease. Recognition of an unrecognized problem militates for patentability. See A and B4 above.

6. If Conte's release rate profile and basis for utility are not novel, then the essence of his invention may relate to his formulations per se. In this regard, the formulations of the present invention differ significantly from those of Conte. For example, this invention teaches a capsule dosage form not suggested in Conte's patent as well as a bilayer or multilayer tablet.

Repeat Request for Constructive Assistance.

Since Applicant has amended the claims of this application so that they are narrow, proper, novel and unobvious, it is submitted that this application is in condition for allowance. Such action is respectfully requested. If for any reason, this application is not believed to be in full condition for allowance, Applicant once again respectfully requests suggestions of the Examiner pursuant to MPEP 706.03(d) and 707.07(j) in order that he can place this application in allowable condition as soon as possible.

Respectfully submitted,

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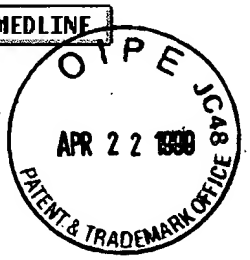
Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, DC 20231, on the date below.

Date: April 19, 1999 Alan Ackerman



J Int Med Res 1982;10(2):126-8

Comparative bioavailability of d-pseudoephedrine from a conventional d-pseudoephedrine sulfate tablet and from a repeat action tablet.

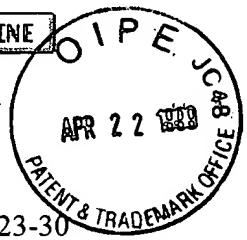
Lin C, Lim J, Symchowicz S

The bioavailability of a single dose of d-pseudoephedrine sulfate administered to male volunteers in repeat action tablet form (60 mg d-pseudoephedrine sulfate in the coat and 60 mg d-pseudoephedrine sulfate in the core) was compared with the bioavailability of an equivalent quantity of the drug given as two 60 mg conventional tablets, one given at 0 hour and the second 6 hours later. There was no significant difference (P less than 0.10) between the conventional tablets and the repeat action tablet formulation in area under the plasma concentration-time curve and the maximum plasma concentration of d-pseudoephedrine. Based on the data, we conclude that the repeat action tablet formulation and the conventional tablet are bioequivalent.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 7067924, UI: 82165387



J Clin Pharmacol 1996 Oct;36(10):923-30

Influence of food on the oral bioavailability of loratadine and pseudoephedrine from extended-release tablets in healthy volunteers.

Nomeir AA, Mojaverian P, Kosoglou T, Affrime MB, Nezamis J, Rodwanski E, Lin CC, Cayen MN

Department of Drug Metabolism, Schering-Plough Research Institute, Kenilworth, NJ 07033, USA.

The effect of a high-fat breakfast on the bioavailability of the components of an extended-release tablet containing 10 mg loratadine in the immediate-release coating and 240 mg pseudoephedrine sulfate in the extended-release core was studied in 24 healthy male volunteers in a single-dose, two-way crossover study. The drug was administered after a 10-hour overnight fast or within 5 minutes of consuming a standardized high-fat breakfast. Serial blood samples were collected over a 48-hour period, and plasma was analyzed for loratadine and its active metabolite descarboethoxyloratadine (DCL), and pseudoephedrine. For pseudoephedrine, maximum concentration (Cmax) and area under the concentration-time curve extrapolated to infinity (AUCzero-infinity) were similar after both treatments, indicating no relevant food effect on the bioavailability of pseudoephedrine. Also, the absorption profiles of pseudoephedrine (from Wagner-Nelson analysis) were similar for the fed and fasted treatments, indicating no apparent differences in absorption. Plasma concentration-time profiles and values for Cmax and AUCzero-infinity of DCL were similar for the two treatments, indicating no relevant food effect on the pharmacokinetics of DCL. In contrast, for loratadine, administration with food resulted in a significantly increased mean Cmax (53%) and AUC from time zero to the final quantifiable sample (AUCif) (76%). However, the resultant Cmax and AUC of loratadine under fed conditions were well below those previously obtained at steady-state after multiple-dose administration of loratadine (40 mg/day) that were shown to be safe and well-tolerated in several clinical studies. The effect of food on the bioavailability and pharmacokinetic profiles of the components of a combination loratadine/pseudoephedrine extended-release tablet is not likely to be clinically significant.

PMID: 8930779, UI: 97084436